Neoplasia III (Epidemiology) and IV (Cancer Pathogenesis)  
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Neoplasia Outline

- Tumor nomenclature
- Tumor characteristics
- Epidemiology
Cancer Incidence

• Every year: 1.5 million new cases of cancer, >500,000 cancer deaths
• Cancer is 2\textsuperscript{nd} leading cause of death (after heart disease)
• Most common cancers
  • Men: Prostate
  • Women: Breast
• Deadliest cancers
  • Men: Lung
  • Women: Lung
Environmental Carcinogens

- Sunlight: skin cancer
- Smoking: lung cancer
- Alcohol: liver, breast cancers
- HPV: cervical carcinoma
Three Types of Hereditary Cancer

- Familial cancers
- Inherited cancer syndromes
- Syndromes of defective DNA repair
Familial Cancers

• Most cases of cancer are “sporadic” (random)
• A small number are “familial” (related to particular germline gene mutations)
• Example: certain BRCA1 gene mutations increase risk of breast, colon, ovary, and pancreatic cancers
• Familial cancers occur earlier and are more aggressive than their sporadic counterparts
Inherited Cancer Syndromes

• Usually autosomal dominant
• Each has a specific gene mutation that increases risk of getting *multiple* cancers
• Example: Li-Fraumeni syndrome
  • mutation in p53 gene
  • 25x increased risk of getting sarcomas, breast cancer, leukemia, and brain tumors, usually before age 50
Syndromes of Defective DNA Repair

- Inherited mutations in genes encoding DNA repair systems
- Greatly enhance the occurrence of mutations in other genes (“genomic instability”)
- Example: xeroderma pigmentosum
  - mutations in genes in “nucleotide excision repair” pathway (fixes UV-damaged DNA)
  - Extreme sensitivity to sun; markedly increased risk of skin cancer (in childhood!)
Neoplasia Outline

• Tumor nomenclature
• Tumor characteristics
• Epidemiology
• Cancer pathogenesis
What causes cancer?
What causes cancer?

Non-lethal genetic damage.
Hallmarks of Cancer

- Autonomic cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
- Ability to invade and metastasize
- Evasion of immune detection
- Altered metabolism
- Angiogenesis
- Resistance to growth-suppressing signals
- Evasion of apoptosis
Autonomous Cell Growth

• Proto-oncogene: a normal gene whose product promotes cell growth.

• Oncogene: a mutated proto-oncogene. Causes tumor cell to grow autonomously.

• Oncoprotein: the product of an oncogene.
The RAS Gene

- RAS is a signal transduction protein
- Mutated RAS is always on...
- ...therefore, always transducing signals...
- ...therefore, cell is always dividing.
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
Resistance to Growth-Suppressing Signals

• Tumor suppressor gene: a normal gene whose product suppresses the cell cycle (like brakes on a car).
• Mutate these guys, and you lose the brakes!
• Must mutate both copies of the gene to cause tumors.
The Retinoblastoma (RB) Gene

- RB gene product stops cell at $G_1$ checkpoint
- Mutant RB is inactive; lets cells pass through $G_1$!
- Patients with two mutated RB genes have way, way high risk of retinoblastoma (and an increased risk of getting other tumors).
The Cell Cycle

- **Chromosome duplication (S)**
- **G0** (resting phase)
- **G1** (growth phase)
- **S** (DNA synthesis phase)
- **G2** (growth phase)
- **M** (mitosis phase)

**Check for DNA damage (G1/S checkpoint)**

**Check for damaged or unduplicated DNA (G2/M checkpoint)**
Autonomous cell proliferation

Resistance to growth-suppressing signals

Evasion of apoptosis

Hallmarks of Cancer
Evasion of Apoptosis

• Many proteins are involved in apoptosis:
  • p53
  • Fas (the “death receptor”)
  • Executioner caspases
  • BCL2 protein family

• If genes for these proteins are mutated, the cell will be able to avoid killing itself.
The p53 Gene

- Nickname for p53: “guardian of the genome”
- If a cell’s DNA is damaged, p53 causes a pause in the cell cycle (via RB), so DNA can be repaired.
- If DNA damage is irreparable, p53 causes the cell to undergo apoptosis.
- Most human tumors have p53 mutations!
p53 activated
- cell cycle arrest
  - DNA damage
  - p53 activated
  - Successful repair
    - Normal cells
  - Repair fails
    - Apoptosis

p53 not activated
- no cell cycle arrest, no DNA repair
  - DNA damage
  - p53 not activated
  - Malignant tumor
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
Immortality

• Normal cells can only undergo 60-70 doublings
• Main reason: telomere shortening!
• Stem cells and cancer cells use telomerase to maintain telomere length and keep replicating.
Telomeres

As cells divide over time...
Binding of telomerase

Extension of 3' end

DNA polymerase completes lagging strand
A simple plan for measurably younger cells that may help you live a longer, healthier life

WE GIVE YOU EVERYTHING YOU NEED TO SUCCEED

A monthly smart-supplement regimen, plus before & after DNA tests to measure the improvement in your cells' biological age based on changes in their telomere length

1. BASELINE DNA TEST
2. TAKE DAILY
3. REAL RESULTS:
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
- Angiogenesis
Angiogenesis

- Tumor cells need blood too!
- Can’t grow >1-2 cm without new vessels
- Tumor cells eventually learn how to stimulate angiogenesis
- Lots of cytokines involved (i.e., VEGF)
Tumor cells surrounding new vessel
Autonomous cell proliferation
Resistance to growth-suppressing signals
Evasion of apoptosis
Immortality
Ability to invade and metastasize
Angiogenesis
Ability to Invade and Metastasize

- To do this, tumor cells must:
  - Loosen contacts between cells
  - Degrade extracellular matrix
  - Migrate away from the original site
- Some tumors lodge in nearest capillary bed
- Some tumors show tropism
Tumor cells surrounding and invading vessel
Tumor cells now within vessel
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
- Ability to invade and metastasize
- Altered metabolism
- Evasion of immune detection
- Angiogenesis

Cell illustration with arrows pointing to each hallmark.
Autonomous cell proliferation
Resistance to growth-suppressing signals
Evasion of apoptosis
Evasion of immune detection
Altered metabolism
Ability to invade and metastasize
Angiogenesis
Immortality

Hallmarks of Cancer
Grading and Staging

- Used for malignant tumors
- Useful for determining treatment and prognosis

**Grading**
- Tells you how nasty the tumor looks (use microscope)
- Somewhat useful

**Staging**
- Tells you how far the tumor has spread (use imaging)
- Very useful
Grading system for breast cancer

Tubules
- lots of tubules: 1
- some tubules: 2
- rare tubules: 3

Pleomorphism
- small, uniform cells: 1
- larger, less uniform cells: 2
- markedly pleomorphic cells: 3

Mitoses
- 0-9 mitoses/10 hpf: 1
- 10-19 mitoses/10 hpf: 2
- ≥20 mitoses/10 hpf: 3

Add all points together

Grade | Score | 5y survival
--- | --- | ---
Low grade | 3-5 | >95%
Intermediate grade | 6-7 | 80%
High grade | 8-9 | 60%
Low grade breast cancer
High grade breast cancer
TNM staging system for non-small cell lung cancer

T=Tumor
Tis – in situ tumor
T1 – small tumor
T2 – larger tumor
T3 – larger or invasive tumor
T4 – very large/very invasive

N=Nodes
N0 – no lymph node involvement
N1 – a few regional nodes
N2 – lots of regional nodes
N3 – distant nodes

M=Metastases
M0 – no metastases
M1 – metastases
## TNM staging system for non-small cell lung cancer

<table>
<thead>
<tr>
<th>Overall stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Treatment</th>
<th>5y prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>Surgery only</td>
<td>75%</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1 or T2</td>
<td>N0</td>
<td>M0</td>
<td>Surgery ± radiation</td>
<td>50%</td>
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<tr>
<td>Stage II</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
<td>Surgery and radiation ± chemotherapy</td>
<td>30%</td>
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<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>T1 or T2</td>
<td>N2</td>
<td>M0</td>
<td>Chemotherapy ± radiation to debulk</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1 or N2</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
<td>Maybe surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Palliative care</td>
<td>&lt;2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maybe chemo or radiation</td>
<td></td>
</tr>
</tbody>
</table>
Grading and Staging

Grading = microscopic

Staging = clinical

Staging is more useful.